REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

I. Introduction

Claims 1-26 and 33-54 are pending in this application. Claims 1, 37 and 53 are amended. Support for the amendment may be found throughout the specification, such as on Pages 5 and 10 of the specification. Non-elected claims 55-60 are cancelled without prejudice or disclaimer. No new matter is added. Claims 6-10, 33, 38, 39, 41, 43, 44, 45, 48, 51, 52 and 54 are withdrawn from consideration. Applicants respectfully request that withdrawn dependent claims be rejoined upon allowance of the independent claim from which they depend.

II. The Rejections Should Be Withdrawn

Claims 1-5, 11-13, 15, 17-26, 34, 35, 37, 40, 42, 43, 46, 47, 49, 50 and 53 are rejected under § 103(a) as being obvious over Altmann in view of Thundat. Claims 14 and 36 are rejected under § 103(a) as being obvious over Altmann in view of Thundat and further in view of Chui. Claim 16 is rejected under § 103(a) as being obvious over Altmann in view of Thundat and further in view of Lee. These rejections are respectfully traversed.

A. Claims 1, 37 and 53

Claims 1 and 53 recite a detector or means for measuring a damping of resonance motion of a resonator driven by the driver element in response to a molecular binding event on the resonator, respectively. Claim 37 recites a detector for measuring a damping of resonance motion of the resonator driven by the driver element in response to a molecular

binding between the at least one first resonator and the substrate or the second mechanical resonator. Neither Altmann nor Thundat teach these limitations.

1. Thermal Fluctuation Measurement of Col. 17 & Fig. 5 of Altmann

The Office Action refers to col. 17, lines 40-53 of Altmann. However, Altmann does not teach or suggest measuring damping of resonance motion of the resonator driven by the driver element in response to a molecular binding event on the resonator in col. 17, lines 40-53.

Column 17, lines 40-53 (i.e., the embodiment of Figure 5) of Altmann state as follows:

> Instead of an oscillation of the cantilever by external driving, one can also use the thermal noise, i.e., thermal position fluctuations of the cantilever, to obtain information about the interaction between the cantilever and the sample surface.
>
> FIG. 5, in diagram a), shows a frequency spectrum representing thermally induced vibrations of a cantilever at a distance 1000 nm of a surface. Diagram b) shows a corresponding positional autocorrelation function. Diagram c) shows a corresponding positional autocorrelation function for a distance of only 100 nm. From the measurement data, a number of parameters characterizing the thermally induced vibrations of the cantilever may be calculated, for example, a resonance frequency and a damping coefficient. [emphasis added]

Thus, in this embodiment, Altmann teaches to replace an externally driven cantilever with a cantilever that fluctuates due to thermal noise. A damping coefficient of the cantilever which fluctuates due to thermal noise may be determined.

However, Altmann does not teach or suggest measuring a damping of resonance motion of the resonator driven by the driver element in response to a molecular binding event on the resonator, as recited in the claims of the present application, for at least two reasons.

First, Altmann expressly teaches to replace the externally driven cantilever (driven by a driver element) when measuring the damping coefficient due to thermal fluctuations. Thus, Altmann teaches away from using a cantilever driven by a driver element when measuring the damping coefficient.

Second, Altmann does not teach or suggest that the damping coefficient is measured in response to a molecular binding event. In other words, Altmann does not indicate that the thermally induced vibrations are caused by the molecular binding event. Thus, Altmann does not enable or teach one of ordinary skill in the art how to determine the damping coefficient due to a molecular binding event.

2. Intra-Molecular Force Spectroscopy of Col. 16-17 & Fig. 4b

Page 14 of the Office Action asserts that col. 16 of Altmann teaches measuring molecular binding events. Applicants respectfully submit that the embodiment of Altmann in col. 16 noted in the Office Action is directed to measuring molecular binding events of a cantilever that is not being driven at a certain frequency. Therefore, Altmann fails to teach or suggest measuring a damping of resonance motion of the resonator driven by the driver element in response to a molecular binding event on the resonator.

For example, col. 16, lines 15-17 of Altmann states: "The molecules bound to the AFM probe can then be used as chemical sensors to detect forces between molecules on the tip and target molecules on a surface." (emphasis added). Col. 16, lines 48-49 of Altmann states: "FIGS. 4a) and b) show schematically examples of force spectroscopy measurements." Thus, the measurements described in col. 16, lines 8-63 are inter-molecular force spectroscopy measurements.

Col. 17, lines 15-28 explains that the force spectroscopy measurements involve a cantilever that is not driven by a driver element. Specifically, col. 17, lines 15-17 explain that "FIG. 4b) shows a schematic example of an intra-molecular force spectroscopy measurement result." Thus, in the force spectroscopy method described col. 17, lines 15-28 and illustrated in Figure 4b of Altmann, a biofunctionalized cantilever is brought near a biofunctionalized

surface. The cantilever is then retreated from the surface to stretch biomolecules between the surface and the cantilever. The tension forces acting on the cantilever are then recorded.

However, in this method, the cantilever is not oscillated at a certain frequency. This is clearly shown in Figure 4b of Altmann. Therefore, since the cantilever is not being osciallated at a certain frequency, it is impossible to measure the damping of resonance motion in this method.

Thus, when Altmann's teachings are viewed as a whole and the force spectroscopy method described in column 16 and in column 17, lines 15-27 and shown in Figure 4b of Altmann is considered as a whole, it becomes clear that Altmann teaches to detect molecular binding effects on cantilevers that are <u>not</u> driven by a driver element. Thus, the damping of resonance motion due to a molecular binding event is not measured in the method of Altmann.

3. AFM Imaging Method of Col. 17 & Fig. 4c

Applicants note that a different (third) method is described in col. 17, lines 29-38 and illustrated in Figure 4c of Altmann. In this method, the cantilever is oscillated at a given frequency to obtain information about the interaction between the cantilever and the substrate. This is a typical atomic force microscopy (AFM) imaging method in which a scanned, oscillating cantilever AFM probe is used to image a surface of the substrate.

However, in this method, there is no molecular binding event between the cantilever and a biomolecule. In other words, the distance between the cantilever and the substrate is measured. The cantilever is not biofunctionalized and there are no molecular binding events on the cantilever that are being measured. Thus, the method of Figure 4c of Altmann also does not provide measurement of damping motion <u>in response to a molecular binding event on the resonator</u> because there is no molecular binding event on the cantilever.

4. Summary

In summary, Altmann teaches three separate and distinct measurement methods. In the thermal fluctuation measurement method of Figure 5 and col. 17, lines 40-53, there is no externally driven cantilever and no apparent molecular binding event. In the intra-molecular force spectroscopy method of Figure 4b, col. 16 and col. 17, lines 15-27, the cantilever is biofunctionalized but is not oscillated. Thus, damping of resonance motion is not measured. In the AFM surface imaging method of Figure 4c and col. 17, lines 29-38, the cantilever is oscillated but not biofunctionalized. There are no molecular binding events on the cantilever and damping of resonance motion due to the molecular binding events are also not measured.

There is no motivation in Altmann to somehow combine these different methods. Thus, Altmann does not teach or suggest detector or means of claims 1, 37 and 53.

Thundat was relied upon merely for the teaching of the size of the cantilever. As noted in the response filed June 9, 2005, Thundat also does not teach or suggest measuring damping of resonance motion. Therefore, even if there was motivation to combine Altmann and Thundat, the combination would not teach or suggest all elements of claims 1, 37 and 53 because neither Altmann nor Thundat teach measuring a damping of resonance motion of the resonator driven by the driver element in response to a molecular binding event on the resonator.

B. Claim 47

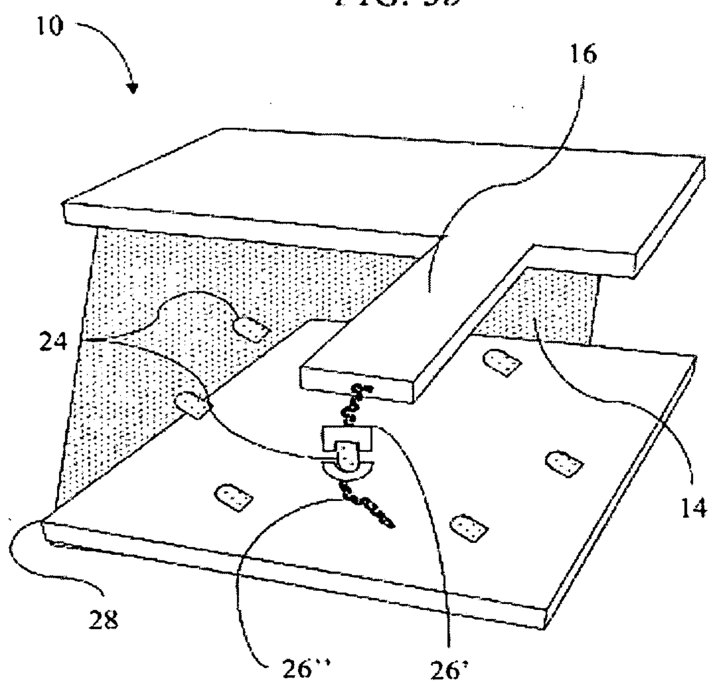
Claim 47 recites "a substrate or a second mechanical resonator which is disposed within the reservoir, wherein the substrate or the second resonator is biofunctionalized with a second receptor or a second ligand, and wherein the first receptor or ligand and the second receptor or ligand are capable of binding to a third receptor or a third ligand in a solution such that the third receptor or ligand binds to both the first receptor or ligand and to the second receptor or ligand at a same time." In other words, claim 47 recites that the cantilever(s) and/or the substrate are biofunctionalized with receptor or ligand which binds to a third receptor or ligand from the solution other than the receptors or ligands that coat the

cantilever(s) and/or the substrate. Thus, the receptors or ligands on the cantilever(s) and/or the substrate do not bind to each other, but instead bind to some other third receptor or ligand from the solution.

A non-limiting example of this configuration is illustrated in Figure 3B of the present application, in which the third ligand 24 binds to the receptor 26' on the cantilever and to the receptor 26" on the substrate. This third ligand 24 binds to the receptors 26' and 26" to cause the cantilever 16 to become bound to the substrate 28. However, the third ligand is not directly bound to cantilever 14 or to the substrate 28.

Figure 3B of the present application is reproduced below:

FIG. 3b

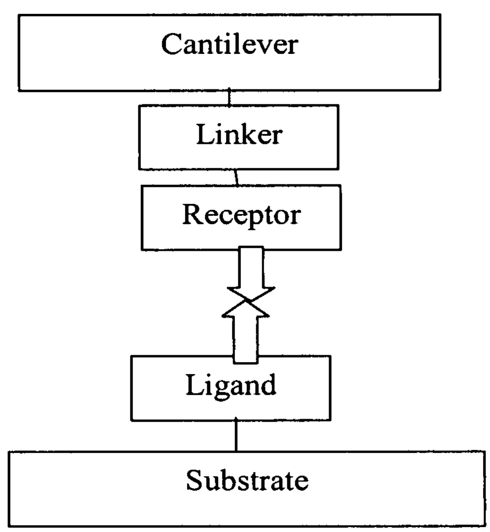


In contrast, Altmann teaches a cantilever which is biofunctionalized with a receptor which binds directly to the ligand on the substrate (i.e., a ligand-receptor pair), as noted in col. 16, lines 19-22. Altmann does not teach or suggest biofunctionalizing the cantilever with a receptors which binds to a separate third ligand from the ligand on the substrate. In other

words, with reference to Figure 3B above, the device of Altmann would have a receptor 26' bound directly to a ligand 26", but would lack the ligand 24 which is not bound to either the substrate or the cantilever.

Page 10 of the Office Action notes that Thundat teaches linker molecules, such as poly-L-lysine in col. 4, lines 10-14. However, such linker molecules are only used to attach the detector molecules of Thundat to the cantilever of Thundat.

Thus, even if there was motivation to combine Altmann and Thundat, then the resulting device would comprise: a cantilever of Altmann or Thundat coated with a linker, a receptor of Altmann which is bound to the linker, and a substrate of Altmann which is coated with a ligand. The ligand is adapted to attach to the receptor. In other words, the cantilever of Altmann + Thundat would be pre-coated with the linker and receptor, while the substrate of Altmann + Thundat would be pre-coated with the ligand. The ligand and receptor would bind to <u>each other</u>, not to some third moiety from an analyte solution, as shown in the schematic below:



Thus, the device of Altmann + Thundat would not be adapted to detect attachment of a third species from the solution (such as ligand 24 shown in the Figure 3b of the present application and reproduced above) which would bind to both the ligand and receptor located on different surfaces. Thus, the device of Altmann + Thundat would not contain "the first receptor or ligand and the second receptor or ligand are capable of binding to a third receptor or a third ligand in a solution such that the third receptor or ligand binds to both the first receptor or ligand and to the second receptor or ligand at a same time," as recited in claim 47.

C. Dependent Claims

Dependent claims 14, 16, 36 and 49 are rejected under § 103(a) as being obvious over Altmann in view of Thundat and further in view of various tertiary references. This rejection is respectfully traversed. Applicants respectfully submit that these tertiary references were applied only against the dependent claims and do not cure the deficiencies of Altmann and Thundat with respect to the independent claims.

III. Conclusion

Applicants submit that the application is now in condition for allowance. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 6/7/07 By [signature]

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 945-6090
Facsimile: (202) 672-5399

Leon Radomsky
Attorney for Applicant
Registration No. 43,445